
UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
PARULA MEHTA, MARSHA GRAHAM,
and ANLOUISE POMERANTZ

Appeal No. 2006-0757
Application No. 09/701,979[1]
Technology Center 1600

ON BRIEF

Before: SCHEINER, ADAMS, and GREEN, *Administrative Patent Judges.*

SCHEINER, *Administrative Patent Judge.*

ORDER REMANDING TO THE EXAMINER

Appellants appeal from a final rejection of claims 1, 2, and 4-13 under 35 U.S.C. § 134. We have jurisdiction under 35 U.S.C. § 6(b). On

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[1] Application filed February 12, 2001. The present application is a national stage entry of PCT/US99/12263, filed June 2, 1999, which claims priority from Provisional Application 60/087,673, filed June 2, 1998. The real party in interest is Ventana Medical Systems, Inc.

consideration of the record, we find that this case is not in condition for a decision on appeal. Accordingly, we remand the application to the Examiner to consider the following issues and to take appropriate action.

BACKGROUND

Histochemical staining uses chemical dyes to make cellular substances or structures in an organism or tissue more visible for identification. Specification, page 1. Many histochemical staining solutions, although prepared from "component solutions [which] are stable for long periods" (*id.*, page 2, lines 22-23), are photolabile, heat labile, or otherwise "unstable, toxic, and generally messy and difficult to work with" once combined into a working solution (*id.*, lines 2-3; page 5, line 1).

According to Appellants, a staining solution is "unstable" if it "exhibits diminished capacity to stain the target organism or tissue, upon standing for any period of time, even as little as one hour" (*id.*, page 4, lines 23-25), and this "instability may manifest itself by the appearance of precipitates or films in the staining solution" (*id.*, page 2, lines 7-8) which "negatively affect[ ] the staining of the tissue and therefore decrease the accuracy of histochemical testing" (*id.*, lines 11-12).

As further explained by Appellants, "[s]ome individual components of [a] stain are made of 'sub-components'. If a final formulation of a solution

cannot be stored until it is needed for use, then the separate ingredients must be made into 'stock solutions' and combined immediately before use. The combined solution is not 'stable', so it must be used within a short time, before it degrades and does not perform its function in the staining procedure. This 'unstable' combined solution is called a 'working solution'" (*id.*, page 5, lines 10-15). A "stable" solution, on the other hand, "can be stored and re-used, . . . does not need to be made fresh prior to use[,]" and preferably, "has a shelf-life of at least one week" (*id.*, page 4, lines 20-22).

Inaccurate results can be avoided by preparing unstable working solutions on a daily basis, but "daily preparation of fresh histochemical staining solutions is time consuming" and "costly[,] since expensive reagents . . . may be squandered if staining solution is prepared and not used by the end of the day" (*id.*, page 2, lines 14-15).

The claimed invention is an automated histochemical staining method that avoids these problems by applying the stable components of an unstable staining solution sequentially and directly to a biological sample. That is, the stable components of the unstable solution are not premixed, but are "kept in separate containers and only mixed after placement of each solution successively on the biological material of interest." *Id.*, page 4, lines 11-12. In a preferred embodiment, "at least two stable solutions that together

comprise an unstable staining solution" are "sequentially deliver[ed] . . . to a biological sample of interest on a planar surface" (*id.*, page 3, lines 11-13) and "the solutions are mixed . . . by applying a gas stream to the . . . stable solutions on the biological material" (*id.*, lines 22-25). Specific applications described in the specification include silver staining, iron staining, trichrome staining, and mucicarmine staining. *Id.*, pages 3, 6-8, and 12-21.

STATEMENT OF THE CASE

The Examiner rejected claims 1, 2, and 4-13 under 35 U.S.C. § 103(a).

Claim 1, the broadest independent claim on appeal, reads as follows:

> 1. An automated method for staining biological materials on a slide, comprising:
>
> a) providing at least a first and second stable solution, wherein the at least first and second stable solutions form an unstable staining solution when combined;
>
> b) providing a slide, wherein a biological material to be stained is present on the slide; and
>
> c) sequentially applying the at least first and second stable solutions to the biological material on the slide using an automated delivery system to form an unstable staining solution in contact with the biological material.

The prior art relied on by the Examiner in rejecting the claims on appeal is:

McCormick	US 3,431,886	Mar. 11, 1969
Stokes	US 5,318,795	Jun. 7, 1994
Copeland	US 5,650,327	Jun. 22, 1997

Joseph F.A. McManus & Robert W. Mowry, *Staining Methods, Histologic and Histochemical*, Paul B. Hoeber, Inc., New York, pages 124-151, 223-245, and 361-372 (1960).

The Examiner rejected claims 1, 2, and 4-13 under 35 U.S.C. § 103 as unpatentable in view of the combined teachings of McCormick, Copeland, McManus, and Stokes.

As characterized by the examiner:

- Copeland describes an automated "method for the staining of [ ] specimens through the application of reagents thereto . . . and teaches mixing of reagents on the slide surface using a gas stream-induced vortex" (Examiner's Answer, page 5);

- McCormick describes "an automated method for . . . sequential application . . . of a plurality of [ ] different solutions to [a] specimen[,]" but does not describe "sequential application . . . of a plurality of stable solutions, which solutions when mixed create an unstable staining solution" (*id.*, page 4);

- Stokes describes an automated staining method wherein "multiple reagents may be applied as part of a single staining step" (*id.*, page 5), and

- McManus describes mixing unstable staining solutions "just prior to use from stable stock reagents" (*id.*).

The examiner argues that "the term 'reagent' as used in the disclosures would include two or more reagent solutions combined to form a third solution" (*id.*, page 5), and "it would have been obvious . . . to mix the reagents of McManus on the slides" because "Copeland and Stokes teach the mixing of reagents on the slide surface," and "McManus suggest[s] the mixing of reagents to form the stains immediately prior to use" (*id.*, page 6).

Appellants, on the other hand, emphasize that all of the unstable staining solutions discussed by the examiner are mixed before they are applied to biological materials, and none of the prior art relied on by the examiner "disclose[s] separately applying two stable ingredients of an unstable staining solution to a biological sample and thereafter forming an unstable staining solution in contact with the biological sample" as required by the claims. Appeal Brief, page 7.

Appellants' point is well taken. In our opinion, the examiner has not squarely addressed this requirement of the claims. The examiner argues that the prior art "does not preclude those in the art from understanding that [ ] stains may be mixed, using the mixing process disclosed by [Copeland], from sequentially added components that together form the reagent" (Examiner's Answer, pages 7-8), and that McManus "suggest[s] that the closer to the point of staining [the stable reagents] are mixed the better" (*id.*,

page 8). Maybe so, but the issue is whether the prior art relied on by the examiner would have suggested refraining from pre-mixing unstable working solutions altogether.

The fact is that the examiner has not identified any portion of any reference that describes mixing stable components directly on a sample to form an unstable histochemical staining solution - manually or automatically. The unstable staining solutions discussed by the examiner are all mixed before being applied to the sample. Thus, one would not arrive at the claimed invention merely by combining the references, or merely by automating the staining protocols described by McManus.

That is not to say that the prior art cited by the examiner is not relevant to the patentability of the claimed invention. Copeland, in addition to describing an automated apparatus and method for vortexing reagents directly on a biological sample, teaches that the apparatus "can be used for a wide variety of assays, for example automatic immunostaining of tissue sections, in situ DNA analysis, immunoassays such as ELISA, and the like." Col. 1, lines 12-15. Copeland's apparatus can perform "all steps of [an] immunohistochemical assay irrespective of complexity or their order, at the time and temperature, and in the environment needed" and "is cost effective in terms of equipment, reagent and labor costs." Col. 2, lines 29-32.

McCormick describes an automated histochemical staining apparatus and method, as does Stokes. While neither describes an apparatus with the versatility of Copeland's, both references provide evidence that automating standard histochemical staining procedures was conventional in the art. In our view, one skilled in the art would have recognized that Copeland's apparatus could be used to perform any histochemical assay, not only immunohistochemical assays.

Moreover, having studied the record, we believe that there is at least some evidence that combining the stable components of an unstable staining solution directly on a sample was known in the art at the time of the invention. For example, the following references, which were cited by Appellants in the specification "in their entirety" (page 12), but not relied on by the Examiner, appear to describe protocols wherein stable component solutions are applied sequentially and directly to a sample to form an unstable staining solution:

> Dezna C. Sheehan & Barbara B. Hrapchak, *Theory and Practice of Histotechnology,* The C.V. Mosby Co., 2nd ed., 1980.
>
> Anthony E. Woods & Roy C. Ellis, *Laboratory Hisptopathology*, Churchill Livingstone, 1994.

In particular, *Theory and Practice of Histotechnology* describes "mordant hematoxylin staining[,]", which "employs *separate* solutions of mordant and of dye during the staining process" and "direct hematoxylin staining[,]" in which "both the dye and the mordant [are] combined together in a *single* solution during the staining process" (pages 146-47, emphases in original). According to the reference, "[o]ne advantage of mordant hematoxylin methods is that the dye itself can be preceded by a mordant salt that [could] not . . . be used in the same solution in a direct staining method. For example, ferric chloride may be used as a mordant in a mordant hematoxylin method and be followed by a hematoxylin solution containing an ammonium salt as one of its components. *If used in combination, however, the two would form undesirable precipitates of ferric hydroxide*" (page 147, emphasis ours).

Additionally, both *Theory and Practice of Histotechnology* (page 147) and *Laboratory Histopathology* (section 5.2-9) describe the Heidenhain iron hematoxylin staining procedure, in which a stable solution of ferric ammonium sulfate (mordanting solution) and a stable solution of alcoholic hematoxylin are applied sequentially to a biological sample to prevent the formation of precipitates and preserve shelf life of component solutions.

"Separating iron and haematoxylin solutions ensures that the haematoxylin has a long shelf life[.]" (*Laboratory Histopathology*, section 5.2-8).

In summary, there is at least some evidence of record supporting the Examiner's conclusion that the claimed invention would have been obvious to one of skill in the art, but that evidence has not been addressed or presented in a manner that gives Appellants a full and fair opportunity to respond. Accordingly we remand the application to the Examiner to take appropriate action based on the issues discussed above. Any further communication from the examiner containing a rejection of the claims should provide Appellants with an opportunity to respond.

REMANDED

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